Message

From: Soto, Vicki [Soto.Vicki@epa.gov]
Sent: 10/9/2020 1:21:17 PM
To: Shams, Dahnish [Shams.Dahnish@epa.gov]
Subject: RE: Inside TSCA - Chloroprene

Too bad there wasn't the comparison to TSCA

From: Shams, Dahnish <Shams.Dahnish@epa.gov>
Sent: Friday, October 09, 2020 9:18 AM
To: Soto, Vicki <Soto.Vicki@epa.gov>
Subject: Re: Inside TSCA - Chloroprene

HA! Told you. Quote!

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From: "Soto, Vicki" <Soto.Vicki@epa.gov>
Date: Friday, October 9, 2020 at 4:07 AM
To: "Thayer, Kris" <thayer.kris@epa.gov>, "Avery, James" <Avery.James@epa.gov>, "Shams, Dahnish" <Shams.Dahnish@epa.gov>, "Kraft, Andrew" <Kraft.Andrew@epa.gov>, "Persad, Amanda" <Persad.Amanda@epa.gov>, John Vandenberg <Vandenberg.John@epa.gov>, "Kapraun, Dustin" <Kapraun.Dustin@epa.gov>, "Schlosser, Paul" <Schlosser.Paul@epa.gov>, "Davis, Allen" <Davis.Allen@epa.gov>, "Lin, Yu-Sheng" <Lin.Yu-Sheng@epa.gov>
Subject: Inside TSCA - Chloroprene

Key Reviewer Doubts Industry Chloroprene Model 'Ready For Prime Time'

October 8, 2020

The chair of an EPA peer review panel that is weighing a new, industry-funded model the agency is considering using to reevaluate its risk assessment of chloroprene, a chemical used to make synthetic rubber, is raising concerns that the model is not ready for use, heightening questions about whether EPA will set a precedent and agree to the industry request to redo the assessment.

"I think this model, while it's beautiful and it's well thought out, it may not be quite ready for prime time," Ken Portier, a biostatistician retired from the American Cancer Society, told the peer review meeting Oct. 6.

Portier said the physiologically based pharmacokinetic (PBPK) model the peer review panel considered "leaves me with a couple of issues, that while I like the model, I'm still concerned about the utility of the model in a couple of areas, especially in [its] ability to predict certain non-male, non-adult populations."

Portier served as the chairman for an ad hoc panel of modeling and statistical experts that an EPA contractor created to peer review a PBPK model for chloroprene developed by Ramboll consultants.

His role in the Oct. 5-6 peer review meeting follows his run as chairman of EPA's science advisory committee to the agency's Toxic Substances Control Act (TSCA) program, where he led that committee's peer reviews of the first 10 draft risk evaluations EPA conducted following Congress' 2016 reform of TSCA.

EPA is funding peer review of the Ramboll PBPK model after Ramboll's client, Denka Performance Elastomers LLC, the manufacturer of chloroprene in the U.S., challenged the agency's 2010 Integrated Risk Information System (IRIS) assessment of chloroprene through a request for correction (RFC) under the Data Quality Act (DQA).

Denka's concern with the existing IRIS program stems from the stringent risk estimate it crafted for chloroprene in air. When combined with EPA's national air toxics modeling program, the area around its LaPlace, LA, facility was deemed to present a high cancer risk to residents, sparking a lawsuit from a citizens' group and attention from state regulators.

EPA's peer review -- and any rollback or revision of the IRIS risk values that may result -- could set a precedent for any RFCs to IRIS assessments or other programs under the DQA, the Clinton-era law that allows private parties to petition agencies to "correct" actions but which courts have held is unenforceable.

But the review is also politically charged amid growing environmental justice concerns as Denka's facility is surrounded by minority communities that face high levels of exposure to chemical releases from this and other facilities in the area.

After denying Denka's first request in 2018, EPA agreed to reconsider after analyzing the model Ramboll developed and subjecting it to peer review.

EPA's Kris Thayer, director of the IRIS program, said at the meeting Oct. 5 that after EPA receives the peer reviewers' completed report, EPA will evaluate their recommendations and respond to Denka's request for reconsideration. If the agency grants the request, Thayer added, staff will evaluate the model's impact on the 2010 IRIS assessment's conclusions.

Track Data

Portier explained that his reservation with the model's fitness for use is based in part on its ability to track some data from toxicology studies of chloroprene, such as in vitro kinetics studies conducted by Matthew Himmelstein and colleagues comparing different species' dose metrics for lung and liver tumors using an early version of the PBPK model and rodent and human tissues. The studies were published in *Toxicological Sciences* in 2004.

"Himmelstein demonstrated using the PBPK dose metric of chloroprene metabolized in the lung as the dose metric and it was able to harmonize the dose responses in lung tumors in mice and hamsters but they only did it in males and we have some female data that seems to be way off and the model doesn't do a good job of that. It worries me that the model may not do a good job in the young and the newly born," Portier said.

"That worries me . . . in terms of these susceptible subpopulations that EPA is mandated to consider and the rest of us morally want to consider, because those are the ones most susceptible to exposures in the environment."

Portier was presumably referring to the reformed TSCA, which requires EPA to include and consider in its risk evaluations of existing chemicals susceptible subpopulations, such as children, the elderly, or those with pre-existing diseases or genetic makeups that make them more susceptible than the general population to particular exposures.

Portier's concerns echo those of the Natural Resources Defense Council's Jennifer Sass, as well as a trio of academic modeling experts who questioned the model's appropriateness for its proposed use in revising IRIS' chloroprene risk analysis.

In public comments offered at the Oct. 5 meeting, Sass questioned whether the data on which the model is based -- a cohort of older Germans -- is appropriate to apply to the community around the Denka facility.

"Clearly, three German women aged 39 and over do not represent the diverse national population, and even less so the populations of St. John the Baptist and St. Charles, the communities that surround the Denka chloroprene manufacturing facility, and have the highest cancer risks in the country from air pollution, driven largely by chloroprene emissions from Denka," Sass said.

She also warned EPA to "be very cautious about using the in vitro to in vivo extrapolation (or IVIVE) approaches," because IVIVE "hasn't been applied to IRIS before." And she sought to correct claims from one of Ramboll's consultants, Dr. Harvey Clewell, who had stated that EPA's pesticide office was also using a PBPK model to test early life sensitivity. "This isn't quite accurate," Sass said. "It was just sent to a peer review panel a few weeks ago."

She also argued that the IVIVE approaches EPA's pesticides office has used "suffer from significant limitations," including using calculations "based upon the median individual in the general population. This is a completely unacceptable model assumption for no-safe-dose health endpoints like developmental neurotoxicity and carcinogenesis."

"If EPA uses this PBPK model in any way to inform its chloroprene evaluation, EPA must still address all cancer endpoints, and the whole evaluation should go through the rigorous process of a full IRIS assessment," Sass said.

Sass was not alone in her concerns, with Dale Hattis, one of a trio of academics who also filed written comments last August, arguing that the model is flawed and should not be used to reevaluate the IRIS assessment. Hattis and colleagues argued that the Ramboll model is flawed because it assumes that humans and lab mice have identical clearance rates of chloroprene metabolites from their bodies.

In making this assumption, "Ramboll effectively ignored the potential for chloroprene's epoxide metabolites to spend more time in the human body. Since this residence time is a critical determinant of risk, it is likely that use of Ramboll's recommended dose metric, the active metabolites generated per unit time, would underestimate the risk to humans resulting from their slower elimination of chloroprene," wrote Hattis, a research professor at Clark University in Massachusetts; Marco Kaltofen, president of Boston Chemical Data Corp. and an associate research engineer at Worcester Polytechnic Institute; and Keeve Nachman, co-director of the Risk Sciences and Public Policy Institute at Johns Hopkins University, in comments submitted to EPA last August.

Other Panelists

Other members of the panel were less forthcoming than Portier in their views on whether the model is ready for its proposed use.

Panelist Jeffrey Heys, a chemical engineering professor at Montana State University, for example, said he found the Ramboll report's "argument that IVIVE models could hold the potential for better predication of disease risk including cancer -- I find those compelling. I'm impressed by this report and others I've read. I think there's a lot of potential. I think it's a step in the right direction."

But Heys also said "there is enough gaps and uncertainty that I have concerns. I think more needs to be done in this area, more needs to be done on this report."

Another panelist, Jochem Louisse, a toxicology researcher at Wageningen University and Research, in the Netherlands, also called the model "a step forward, much better than standard safety factors from animal data" that EPA and others traditionally use in risk assessment to address uncertainties inherent in risk analysis when there is no chemical-specific information. Louisse, too, noted the model "brings about a lot of uncertainties. I think it's very good how that is trying to be tackled here. Should not be dissuaded from using here. Because it actually shows the uncertainties."

One panelist, Leslie Benet, a bioengineering professor at the University of California-San Francisco, offered a contrasting view to Portier's. "In my mind, [the model] does what we want to predict," he said. "I think EPA can use it."

Because the peer review panel is a lower tier of review conducted by a contractor, rather than an agency advisory committee, the panel does not have to reach consensus in its responses to EPA's charge questions. Instead, EPA will receive a report with final written comments from each of the nine individual experts. The panel manager, Versar's David Bottimore, said that he expects the panel to transmit its final report to the agency sometime in November. -- *Maria Hegstad* (mhegstad@iwpnews.com)

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